Claim Objections

Claim 2 stands objected because of the informalities. Applicants have also amended claim 2 to correct the typographical error. This ground of objection has been obviated.

Rejections Under 35 U.S.C. § 112, second Paragraph

Claims 20-22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action alleges that the limitation "said cloning system" in claim 20 lacks antecedent basis.

Claim 20 has been amended to clarify the limitation. Claims 21 and 22 depend from claim 20. Accordingly, the grounds for the 35 U.S.C. 112, second paragraph, rejection have been obviated and thus, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1, 2, 4, 6, 20-22 and 27-31 stand rejected under 35 U.S.C. 102(b) as being anticipated by Brunelli et al. for the reasons set forth on page 5 of the Office Action.

Claims 1, 6-8, 20-22 and 27-32 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 5,646.037 to Buxton et al. (Buxton) for the reasons set forth on pages 5 and 6 of the Office Action.

Claims 1, 2, 4 and 20 have been amended. Accordingly, Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. Of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).* The identical

invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).* There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic Research & Foundation v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).*

In this case, the vector system of independent Claim 1, as amended, comprises (1) a first arm having a first selectable marker, a first cyclization element, and a first segment homologous to the 5' terminus of a target polynucleotide; and (2) a second arm having a second selectable marker, a second cyclization element, and a second segment homologous to the 3' terminus of the target polynucleotide, wherein at least one arm further comprises an origin of replication.

In contrast, Brunelli describes a series of yeast/*E coli* lamda expression vectors designed for directional cloning of cDNAs and cre/lox-mediated plasmid excision. The cloning vectors of Brunelli do not use homologous recombination technology and, therefore, do not contain a segment homologous to the terminus of a target polynucleotide. Accordingly, Brunelli does not anticipate the present invention because it does not contain all of the elements of claim 1. Applicants further submit that dependent claims 2, 4, 6, 20-22 and 27-31 are not anticipated by Brunelli because these claims depend from claim 1. Therefore, withdrawal of the 35 U.S.C. 102(b) rejection is respectfully requested.

Buxton describes hybrid vectors based on the yeast two micron plasmid. Similar to Brunelli, the hybrid vectors of Buxton do not use homologous recombination technology and, therefore, do not contain a segment homologous to the terminus of a target polynucleotide. Accordingly, Buxton does not anticipate the present invention because it does not contain all of the elements of claim 1. Applicants further submit that dependent claims 6-8, 20-22 and 27-31 are not anticipated by Buxton because they depend from claim 1.

Thus, the grounds for this rejection have been obviated and withdrawal of the 35 U.S.C. 102(b) rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-6, 20-22 and 27-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brunelli in view of US 2002/0170076 (Dymecki) for the reasons set forth on pages 7-8 of the Office Action. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Independent claim 1 of the present invention is described above. One advantage of the present invention is to provide a versatile, recombination approach to the capture, cloning, manipulation, production and delivery of large nucleic acids to a target cell, as set forth in amended Claim 1 (see page 3 of the present specification).

In contrast, Brunelli, as described earlier, teaches yeast/*E coli* lamda expression vectors designed for directional cloning of cDNAs and cre/lox-mediated plasmid excision. The cloning vectors of Brunelli do not use homologous recombination technology. Furthermore, The vectors of Brunelli are **compact** (circa 6 kb) (see page 1309, right col, paragraph 3). In fact, the Brunelli reference teaches away from cloning, manipulation, production and delivery of **large** nucleic acids to a cell.

Dymecki describes a method for producing site-specific recombination of DNA in a transgenic non-human mammal at chromosomal regions containing Flp-recognition sites using homologous recombination technology. Dymecki does not disclose a vector system for capture,

cloning, manipulation, production and delivery of large nucleic acids to a target cell using homologous recombination.

Neither Brunelli nor Dymecki discloses or suggests a system for cloning nucleic acids using homologous recombination presently claimed. Consequently, the advantages provided by the present invention for the capture, cloning, manipulation, production and delivery of large nucleic acids to a target cell are not taught or suggested by the combination of Brunelli and Dymecki. Thus, it is not obvious to one skilled in the art to derive the present invention from the prior art of record.

Moreover, when applying 35 U.S.C. § 103, the Examiner is required to adhere to the following tenets of patent law: (1) The claimed invention must be considered as a whole; (2) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Furthermore, the CAFC in *In re Sang Su Lee* states teaching of references can be combined only if there is some suggestion or incentive to do so. *In re Sang Su Lee* (Fed. Cir. January 18, 2002) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.,* 732 F.2d 1572, 1577 (Fed. Cir. 1984).

In this case, Brunelli provides no desirability and no teaching of making the combination with Dymecki. The Brunelli vectors are designed for easy cloning of cDNAs. Dymecki teaches a method for site specific recombination of DNA in a transgenic non-human animal at particular chromosomal regions containing an FLP-recognition site. DNA containing FLP recombinase and its recombination target FRT is used for site-specific recombination *in vivo* at engineered FRT

sites. The DNA may also contain a transgene for insertion into the genome of a non-human mammal, or a region which directs homologous recombination into the genome of the non-human mammal.

Accordingly, Brunelli provides no motivation to combine a method for cloning cDNAs with a method for site specific recombination of DNA in a transgenic non-human animal. Therefore, a prima facie case of obviousness has not been presented. Applicants further submit that dependent claims 2-6, 20-22 and 27-31 are patentable because they depend from claim 1.

Claims 1-9, 20-22 and 27-32 also stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brunelli and Dymecki and further in view of Buxton for the reasons set forth on pages 9-10 of the Office Action. Applicants respectfully traverse the rejection.

As discussed above, there is no desirability or motivation to combine Brunelli with Dymecki. The hybrid vectors of Buxton do not use homologous recombination technology and do not contain a segment homologous to a target polynucleotide. It follows that, there is no suggestion to further combine Brunelli and Dymecki with Buxton. Furthermore, with respect to the Examiner's statement that Buxton teaches that the target sequences may be a DNA virus, such as Herpes virus, Applicants would like to call the Examiner's attention to the fact that the vector system of Brunelli is specifically designed for speedy cDNA cloning, and one skilled in the art would not use the Brunelli system to clone DNA virus and hence would not be motivated to combine the teachings of Brunelli with those of Buxton. Even if one skilled in the art were to combine Brunelli, Dymecki and Buxton, they would not obtain the invention as claimed. Therefore, Applicants respectfully submits that Brunelli, Dymecki and Buxton do not render the present invention obvious.

Claims 1-11, 20-22 and 27-32 further stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brunelli, Dymecki, Buxton and further in view of Liu et al for the reasons set

forth on pages 10-11 of the Office Action. Claims 1-13, 20-22 and 27-32 further stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brunelli, Dymecki, and further in view of Buxton, Liu and further in view of Crouzet et al for the reasons set forth on pages 10-11 of the Office Action.

As described above, one skilled in the art would not have been motivated to combine Brunelli, Dymecki, and Buxton to render the present invention obvious. Neither Liu, cited by the Examiner as teaching vectors which may comprise sequences from a retrovirus as the target sequence, nor Crouzet cited by the Examiner as teaching a vector comprising an origin of replication and an HIV target sequence, compensate for the lack of disclosure of the claimed vector system for capture, cloning, manipulation, production and delivery of large nucleic acids to a target cell by Brunelli, Dymecki, and Buxton. Moreover, one skilled in the art would not be motivated to combine Brunelli, Dymecki, Buxton, Liu and Crouzet to render the present invention obvious.

Therefore, the references of Brunelli, Dymecki, Buxton, Liu do not support a *prima facie* case of obviousness. The grounds for this rejection have been obviated and withdrawal of the 35 U.S.C. 103 rejection is respectfully requested.

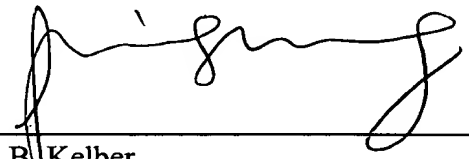
CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Ping Wang, M.D. (Reg. No. 48,328) at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP



Steven B. Kelber
Registration No. 30,073
Attorney of Record

Ping Wang, M.D.
Registration No. 48,328

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085

SERIAL NO. 09/762,476

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MARKED-UP COPY OF AMENDED CLAIMS

1. (Amended) [Vectors] A vector system for capture, cloning, manipulation, production and delivery of large nucleic acids to a target cell comprising:

(a) a first arm having a first selectable marker, [and] a first cyclization element, and a first segment homologous to the 5' terminus of a target polynucleotide; and

(b) a second arm having a second selectable marker, [and] a second cyclization element, and a second segment homologous to the 3' terminus of the target polynucleotide,

wherein at least one arm further comprises an origin of replication.

2. (Amended) The [vectors] vector system of Claim 1, wherein each arm further comprises a rare restriction endonuclease recognition [sit] site.

3. (Amended) The [vectors] vector system of Claim 1, wherein each arm further comprises a polylinker.

4. (Amended) The [vectors] vector system of Claim 1, wherein said first cyclization element is a nucleic acid comprising a first LOX site, and said second cyclization element is a nucleic acid comprising a second LOX site.

6. (Amended) A composition comprising said [vectors] vector system of Claim 1 and a target sequence.

20. (Amended) A eukaryotic host cell comprising said [cloning system] vector system of Claim 1.